Electrocyclization of β-Arylvinyl Ketenimines: Formal Syntheses of the Alkaloid from Marine Origin, 5,8-Dihydro-7-methoxy-1,6-dimethylisoquinoline-5,8-dione, and 3-Ethoxycarbonylrenierol

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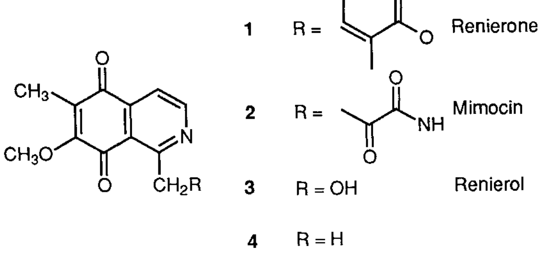
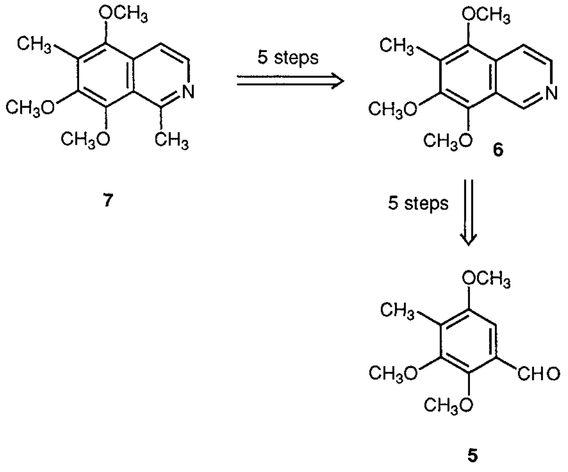
A new six-step synthetic route for the preparation of the alkaloid from marine origin, 5,8-dihydro-7-methoxy-1,6-dimethylisoquinoline-5,8-dione is reported. The method is based on the electrocyclization of the appropriate β-arylvinyl ketenimine, available by aza Wittig reaction of the corresponding vinyl iminophosphorane with (trimethylsilyl)ethenone followed by decarboxylation and further oxidative demethylation. Likewise, this method has successfully been applied to the preparation of the 3-ethoxycarbonylrenierol.

In recent years several naturally occurring isoquinoline quinones have been isolated both from marine sponges and from terrestrial bacteria. Renierone (**1**) is the major antimicrobial metabolite of *Reniera* sp., a bright-blue sponge found near Isla Grande Mexico;[1] mimocin (**2**), a metabolite of *Streptomyces lavendulae*,[2] contains a pyruvamide side chain in place of the angelate ester side chain of renierone (**1**). Renierol (**3**) was isolated from the hard-blue Fijian sponge *Xestospongia caycedoi*[3] and further studies of the metabolites of *Reniera* sp. have resulted in the isolation[4] of 5,8-dihydro-7-methoxy-1,6-dimethylisoquinoline-5,8-dione (**4**). The structural similarity between renierone (**1**), mimocin (**2**), renierol (**3**) and 5,8-dihydro-7-methoxy-1,6-dimethylisoquinoline-5,8-dione (**4**) is striking: all of them have a common skeleton, i.e. 5,8-dihydro-7-methoxy-6-methylisoquinoline-5,8-dione, and differ only in the side chain at C-1 of the isoquinoline ring.



The isoquinoline quinone **4** inhibits human immunodeficiency virus (HIV) reverse transcriptase and also inhibits avian myeloblastosis virus (AMV) reverse transcriptase, but does not inhibit the activity of DNA polymerases α and β.[5]

Of the two syntheses[6] of 5,8-dihydro-7-methoxy-1,6-dimethylisoquinoline-5,8-dione (**4**) previously reported, one of them is based on the formation of the isoquinoline **6** in five steps starting from 2,3,5-trimethoxy-4-methylbenzaldehyde (**5**) by a modified Pomeranz–Fritsch reaction and the introduction of a methyl group at C-1 to give the key intermediate **7** is also achieved in five steps.



In the course of our studies directed towards the synthesis of nitrogen heterocyclic compounds based on heterocyclization reactions of azahexatriene systems, we have developed the so-called aza Wittig/electrocyclic ring closure strategy for the synthesis of isoquinolines.[7] This methodology has been successfully applied to the synthesis of the alkaloids rufescine[8] and aaptamine.[9] We have been interested in developing a reliable iminophosphorane-based route to isoquinoline alkaloids with a methyl substituent at C-1, which could be suitably applied to the synthesis of the key intermediate **7**, successfully used in the total synthesis of the alkaloid **4**.

Condensation of 2,4,5-trimethoxy-3-methylbenzaldehyde[10] with ethyl azidoacetate in the presence of NaOEt at −15 °C provided the α-azidocinnamate **8** in 85% yield. Compound **8** was converted into 3-ethoxycarbonyl-5,7,8-trimethoxy-1,6-dimethylisoquinoline (**11**) in 85% overall yield by a one-flask process involving sequential treatment with trimethylphosphane, (trimethylsilyl)ethenone,[11] heating at 160 °C and chromatographic separation using a silica gel column. The conversion **8**→**11** can be rationalized by an initial Staudinger reaction between the α-azidocinnamate **8** and trimethylphosphane to give the iminophosphorane **9**, which was used without purification for the next step. Aza Wittig reaction of **9** with (trimethylsilyl)ethenone yields the ketenimine **10**, which undergoes electrocyclic ring-closure and further carbon-silicon bond cleavage to give **11**. This compound was converted into the desired 5,7,8-trimethoxy-1,6-dimethylisoquinoline (**7**) by hydrolysis with LiOH in THF/H_2O (40%) followed by decarboxylation in diphenyl ether at 180 °C (62%).

This constitutes a formal total synthesis of the 5,8-dihydro-7-methoxy-1,6-dimethylisoquinoline-5,8-dione (**4**),

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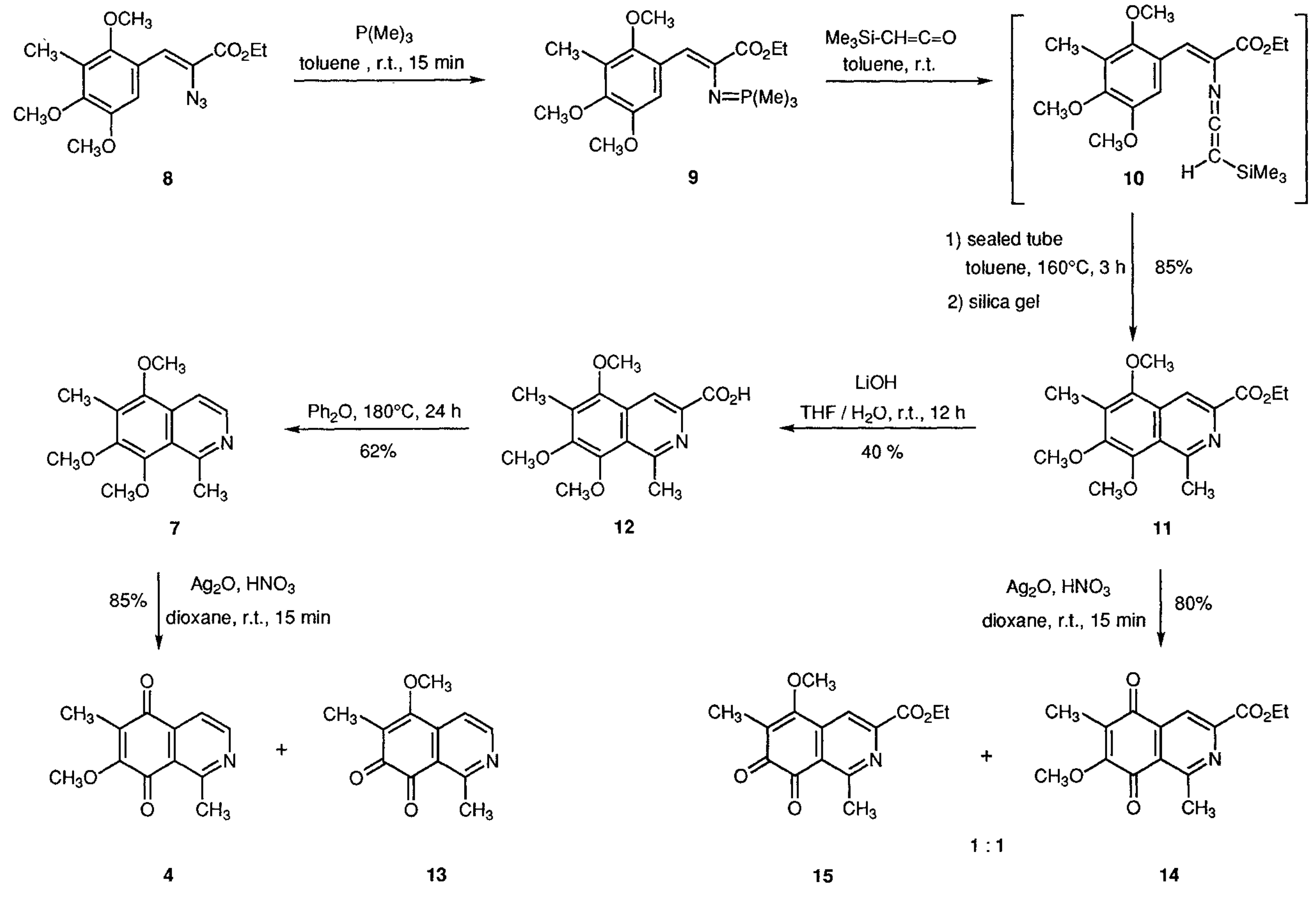
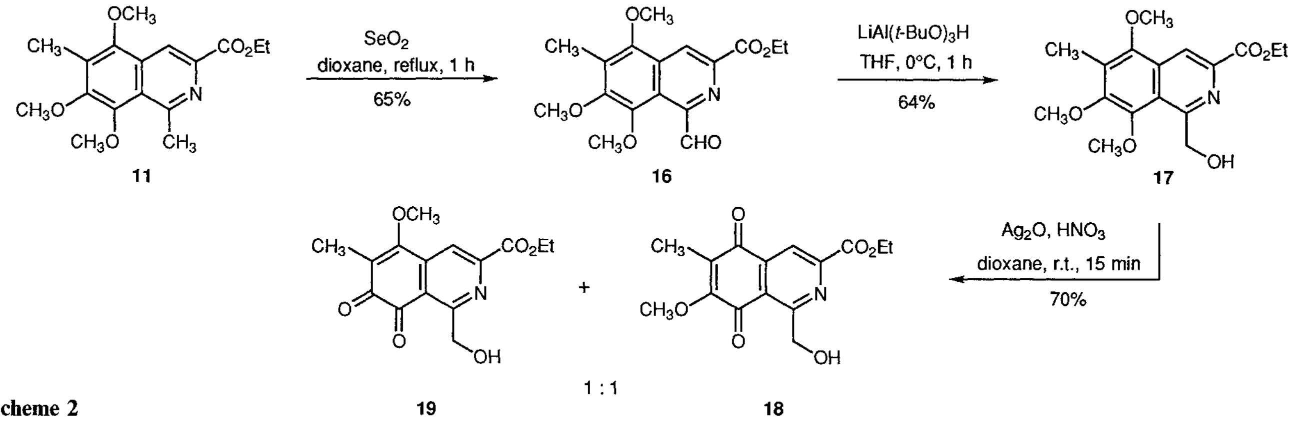


Scheme 1

since **7** may be converted into the target molecule in 50 % yield by Ag_2O oxidation. Likewise, oxidative demethylation of isoquinoline **11** afforded a mixture of quinones **14** and **15** (1:1 ratio) (Scheme 1).

This method has also been applied to the synthesis of a 3-ethoxycarbonyl derivative of the alkaloid renierol (**3**). The 1-methylisoquinoline **11** was converted into the 1-formylisoquinoline **16** in 65 % yield by oxidation with SeO_2. Reduction of **16** with lithium tri-*tert*-butoxyaluminum hydride provided the 1-hydroxymethylisoquinoline **17** in 64 % yield. Oxidative demethylation using the system Ag_2O/HNO_3/dioxane provided the *p*-quinone **18** (35 %) and *o*-quinone isomer **19** (35 %) (Scheme 2).

In conclusion, we have demonstrated that the aza Wittig reaction of the iminophosphorane derived from a substituted α-azidocinnamate with (trimethylsilyl)ethenone affords a convenient entry for the preparation of the corresponding 1-methylisoquinoline, used as key intermediate in the synthesis of the alkaloid 5,8-dihydro-7-methoxy-1,6-dimethylisoquinoline-5,8-dione, and 3-ethoxycarbonylrenierol.



Scheme 2

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All melting points were determined on a Kofler hot-plate melting point apparatus and are uncorrected. IR spectra were obtained as Nujol emulsions or films on a Nicolet Impact 400 spectrophotometer. NMR spectra were recorded on a Bruker AC-200 (200 MHz) or a Varian Unity 300 (300 MHz) spectrometer. Mass spectra were recorded on a Hewlett-Packard 5993C spectrometer. Microanalyses were performed on a Carlo Erba EA-1108 instrument.

Ethyl α-Azido-2,4,5-trimethoxy-3-methylcinnamate (8):
A mixture of ethyl azidoacetate (5.16 g, 40 mmol) and 3-methyl-2,4,5-trimethoxybenzaldehyde (2.10 g, 10 mmol) in anhyd EtOH (20 mL) was added dropwise under N_2 at -15 °C to a well-stirred solution containing Na (0.91 g, 40 mmol) in anhyd EtOH (100 mL). The mixture was stirred at that temperature for 7 h, poured into aq NH_4Cl solution (150 mL) and extracted with Et_2O (3 × 75 mL). The combined organic layers were washed with H_2O (2 × 100 mL), brine (100 mL) and dried ($MgSO_4$). The $MgSO_4$ was removed by filtration and the solvent concentrated to dryness. The resulting solid was recrystallized from EtOH to give **8** (2.73 g, 8.5 mmol); yield 85 %; mp 81–83 °C; yellow prisms.

MS (EI, 70 eV): m/z (%) = 321 (M^+, 5), 220 (100).

IR (Nujol): ν = 2124, 2102, 1706, 1257, 1095, 992, 844 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 1.40 (t, 3 H, J = 7.1 Hz), 2.21 (s, 3 H), 3.69 (s, 3 H), 3.84 (s, 3 H), 3.88 (s, 3 H), 4.37 (q, 2 H, J = 7.1 Hz), 7.27 (s, 1 H), 7.72 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 9.40, 14.16, 55.98, 60.30, 61.62, 62.10, 110.77, 119.56, 121.59 (s), 124.65 (s), 125.20 (s), 148.76 (s), 149.43 (s), 152.52 (s), 163.72 (s).

$C_{15}H_{19}N_3O_5$	calc.	C 56.07	H 5.92	N 13.09
(321.3)	found	56.16	5.74	13.19

3-Ethoxycarbonyl-5,7,8-trimethoxy-1,6-dimethylisoquinoline (11):
To a solution of **8** (0.64 g, 2 mmol) in anhyd toluene (20 mL) was added PMe_3 (2 mL of a 1 M solution) dropwise at r.t. and the mixture was stirred for 15 min. Then, (trimethylsilyl)ethenone (0.23 g, 2 mmol) was added and the resulting mixture was stirred at r.t. for 30 min, then heated in a sealed tube at 160 °C for 3 h. After cooling, the solvent was removed under reduced pressure and the residual material was chromatographed on a silica gel column using EtOAc/hexane (1 : 1, v/v) as eluent to give **11** (0.54 g, 1.70 mmol); yield 85 %; mp 71–72 °C; yellow prisms from Et_2O.

MS (EI, 70 eV): m/z (%) = 319 (M^+, 44), 247 (100).

IR (Nujol): ν = 1713, 1563, 1330, 1259, 1004, 962, 843, 787 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 1.43 (t, 3 H, J = 7.1 Hz), 2.35 (s, 3 H), 3.12 (s, 3 H), 3.85 (s, 3 H), 3.88 (s, 3 H), 3.92 (s, 3 H), 4.47 (q, 2 H, J = 7.1 Hz), 8.50 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 10.04, 14.30, 27.40, 60.23, 60.75, 61.51, 61.85, 116.43, 123.41 (s), 128.57 (s), 129.07 (s), 139.61 (s), 146.18 (s), 150.76 (s), 152.29 (s), 157.77 (s), 165.97 (s).

$C_{17}H_{21}NO_5$	calc.	C 63.95	H 6.58	N 4.38
(319.3)	found	63.83	6.69	4.25

5,7,8-Trimethoxy-1,6-dimethylisoquinoline-3-carboxylic Acid (12):
To a stirred solution of **11** (0.25 g, 0.7 mmol) in THF (15 mL) was added in one portion $LiOH{\cdot}H_2O$ (0.13 g, 3 mmol) in H_2O (5 mL). The mixture was stirred at r.t. for 12 h. After removing the THF under reduced pressure, H_2O (10 mL) was added to the remaining aqueous solution. Then HCl (6 N) was added until pH 5 and the solution was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to dryness to give a solid, which was recrystallized from Et_2O to give **12** (0.09 g, 0.31 mmol); yield 40 %; mp 136 °C; yellow prisms.

MS (EI, 70 eV): m/z (%) = 291 (M^+, 35), 247 (100).

IR (Nujol): ν = 1761, 1599, 1564, 1232, 1123, 998, 903, 846 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 2.41 (s, 3 H), 3.13 (s, 3 H), 3.88 (s, 3 H), 3.96 (s, 3 H), 3.98 (s, 3 H), 7.08 (br s, 1 H), 8.64 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 10.26, 26.83, 60.38, 60.91, 62.08, 115.45, 123.88 (s), 129.30 (s), 130.39 (s), 137.13 (s), 146.63 (s), 151.28 (s), 153.16 (s), 156.85 (s), 165.17 (s).

$C_{15}H_{17}NO_5$	calc.	C 61.85	H 5.84	N 4.82
(291.3)	found	61.98	5.89	4.71

5,7,8-Trimethoxy-1,6-dimethylisoquinoline (7):
A solution of **12** (0.23 g, 0.8 mmol) in Ph_2O (2 mL) was heated to 180 °C for 24 h. After cooling, the mixture was chromatographed directly on a silica gel column using EtOAc as eluent to give **7** as an oil (0.12 g, 0.49 mmol); yield 62 %. All spectroscopic data are identical to those reported in the literature.[6]

Oxidation of Isoquinolines 7 and 11; General Procedure:
The appropriate isoquinoline **7** or **11** (0.2 mmol) and Ag_2O (0.10 g, 0.8 mmol) were taken in a flask containing dioxane (2 mL). Nitric acid (6 N, 2 mL) was added to the mixture, and after stirring at r.t. for 15 min, the resulting mixture was diluted with H_2O (15 mL) and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with brine (3 × 25 mL), dried ($MgSO_4$) and concentrated to dryness to obtain a solid which was chromatographed on a silica gel column with EtOAc/hexane (1 : 1, v/v) to give a mixture (**4**+**13**) or (**14**+**15**), respectively.

5,6-Dihydro-7-methoxy-1,6-dimethylisoquinoline-5,8-dione (**4**) R_f = 0.7) yield 50 %; mp 188–190 °C (Lit.[4] 188–190 °C).

7,8-Dihydro-5-methoxy-1,6-dimethylisoquinoline-7,8-dione (**13**) (R_f = 3) yield 35 %; mp 148–158 °C (dec.) [Lit.[6] 149 °C (dec.)].

3-Ethoxycarbonyl-5,8-dihydro-7-methoxy-1,6-dimethylisoquinoline-5,8-dione (**14**) (R_f = 0.7) yield 40 %; mp 117–118 °C; orange prisms.

MS (EI, 70 eV): m/z (%) = 289 (M^+, 5), 217 (100).

IR (Nujol): ν = 1745, 1737, 1666, 1598, 1307, 1207, 1133, 977, 741 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 1.46 (t, 3 H, J = 7.2 Hz), 2.10 (s, 3 H), 3.06 (s, 3 H), 4.16 (s, 3 H), 4.52 (q, 2 H, J = 7.1 Hz), 8.52 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 9.13, 14.32, 25.79, 61.31, 62.61, 118.76, 124.89 (s), 130.47 (s), 140.10 (s), 151.28 (s), 158.87 (s), 160.80 (s), 163.93 (s), 181.54 (s), 184.16 (s).

$C_{15}H_{15}NO_5$	calc.	C 62.28	H 5.19	N 4.84
(289.3)	found	62.10	5.30	4.71

3-Ethoxycarbonyl-7,8-dihydro-5-methoxy-1,6-dimethylisoquinoline-7,8-dione (**15**) (R_f = 0.3) yield 40 %; mp 134–135 °C; yellow prisms.

MS (EI, 70 eV): m/z (%) = 289 (M^+, 7), 189 (100).

IR (Nujol):ν = 1725, 1695, 1663, 1649, 1334, 1257, 1202, 1137, 952, 721 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 1.48 (t, 3 H, J = 7.2 Hz), 2.15 (s, 3 H), 2.99 (s, 3 H), 4.08 (s, 3 H), 4.53 (q, 2 H, J = 7.1 Hz), 8.25 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 10.07, 14.32, 25.80, 61.62, 62.80, 117.96, 123.34 (s), 126.83 (s), 143.39 (s), 152.32 (s), 162.79 (s), 163.17 (s), 164.22 (s), 179.84 (s), 180.31 (s).

$C_{15}H_{15}NO_5$	calc.	C 62.28	H 5.19	N 4.84
(289.3)	found	62.15	5.32	4.71

3-Ethoxycarbonyl-1-formyl-5,7,8-trimethoxy-6-methylisoquinoline (16):
To a solution of **11** (0.31 g, 1 mmol) in anhyd dioxane (10 mL) was added SeO_2 (0.11 g, 1.05 mmol) and the mixture was stirred at reflux temperature for 1 h. After cooling, the mixture was filtered on Celite and the filtrate was concentrated to dryness, the resulting solid was dissolved in $CHCl_3$ (20 mL) and the solution was filtered. The solvent was removed under reduced pressure and the remaining solid was chromatographed on a silica gel column with EtOAc/hexane (7 : 3, v/v) as eluent to give **16** (0.21 g, 0.63 mmol); yield 65 %; mp 120 °C; colorless needles from $CHCl_3$/hexane.

MS (EI, 70 eV): m/z (%) = 333 (M^+, 100), 261 (96).

IR (Nujol): ν = 1713, 1604, 1329, 1082, 1002, 955 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 1.47 (t, 3 H, J = 7.1 Hz), 2.43 (s, 3 H), 3.89 (s, 3 H), 3.93 (s, 3 H), 4.01 (s, 3 H), 4.53 (q, 2 H, J = 7.1 Hz), 8.76 (s, 1 H), 10.73 (s, 1 H).

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^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 10.44, 14.42, 60.55, 60.66, 62.05, 62.33, 119.75, 122.01 (s), 129.02 (s), 130.93 (s), 140.86 (s), 143.87 (s), 151.25 (s), 152.51 (s), 154.30 (s), 165.40 (s), 192.98.

$C_{17}H_{19}NO_6$	calc.	C 61.26	H 5.71	N 4.21
(333.3)	found	61.01	5.75	4.33

3-Ethoxycarbonyl-1-hydroxymethyl-5,7,8-trimethoxy-6-methylisoquinoline (17):

To a solution of **16** (0.50 g, 1.5 mmol) in anhyd THF (20 mL) cooled to 0 °C was added $LiAl(t\text{-}BuO)_3H$ (0.51 g, 2 mmol). The mixture was stirred at 0 °C for 1 h and then allowed to warm to r.t. The solution was diluted with H_2O (40 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (3 × 20 mL) and dried ($MgSO_4$). After filtration, the filtrate was concentrated to dryness and the residual solid was chromatographed on a silica gel column with EtOAc/hexane (9:1, v/v) as eluent to give **17** (0.32 g, 0.96 mmol); yield 64 %; mp 129 °C; colorless prisms from Et_2O.

MS (EI, 70 eV): *m*/*z* (%) = 335 (M^+, 100), 246 (76).

IR (Nujol): ν = 3335, 1730, 1567, 1331, 1198, 1131, 1032, 999 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 1.47 (t, 3 H, *J* = 7.1 Hz), 2.41 (s, 3 H), 3.91 (s, 3 H), 3.95 (s, 3 H), 3.97 (s, 3 H), 4.49 (q, 2 H, *J* = 7.1 Hz), 5.30 (s, 2 H), 5.65 (br s, 1 H), 8.60 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 10.27, 14.44, 60.35, 60.94, 61.62, 62.14, 64.50, 117.63, 121.45 (s), 128.62 (s), 130.05 (s), 138.39 (s), 145.82 (s), 151.16 (s), 152.67 (s), 157.73 (s), 165.57 (s).

$C_{17}H_{21}NO_6$	calc.	C 60.89	H 6.27	N 4.18
(335.3)	found	60.97	6.35	4.01

Oxidation of 3-Ethoxycarbonyl-1-hydroxymethyl-5,7,8-trimethoxy-6-methylisoquinoline (17):

The method used was the same as described above for the oxidation of isoquinolines **7** and **11**.

3-Ethoxycarbonylrenierol (**18**) (R_f = 0.7) yield 35 %; red oil.

MS (EI, 70 eV): *m*/*z* (%) = 305 (M^+, 17), 203 (100).

IR (Nujol): ν = 3428, 1743, 1730, 1667, 1600, 1377, 993, 880 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 1.46 (t, 3 H, *J* = 7.1 Hz), 2.11 (s, 3 H), 4.18 (s, 3 H), 4.51 (q, 2 H, *J* = 7.1 Hz), 5.22 (s, 2 H), 8.61 (s, 1 H), (OH was not observed).

^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 9.29, 14.28, 61.49, 62.69, 64.20, 119.62, 127.70 (s), 131.13 (s), 140.37 (s), 150.59 (s), 158.38 (s), 160.95 (s), 163.39 (s), 181.21 (s), 183.65 (s).

$C_{15}H_{15}NO_6$	calc.	C 59.02	H 4.92	N 4.59
(305.3)	found	58.80	5.01	4.77

3-Ethoxycarbonyl-7,8-dihydro-1-hydroxymethyl-5-methoxy-6-methylisoquinoline-7,8-dione (**19**) (R_f = 0.4) yield 35 %; red oil.

MS (EI, 70 eV): *m*/*z* (%) = 305 (M^+, 24), 205 (100).

IR (Nujol): ν = 3423, 1725, 1666, 1614, 1213, 1071, 1019 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$/TMS): δ = 1.47 (t, 3 H, *J* = 7.1 Hz), 2.17 (s, 3 H), 4.11 (s, 3 H), 4.52 (q, 2 H, *J* = 7.1 Hz), 5.15 (s, 2 H), 8.34 (s, 1 H), (OH was not observed).

^{13}C NMR (50 MHz, $CDCl_3$/TMS): δ = 10.19, 14.27, 61.64, 62.80, 64.26, 118.86, 124.69 (s), 127.15 (s), 144.09 (s), 151.73 (s), 162.78 (s), 163.69 (s), 164.88 (s), 178.88 (s), 179.35 (s).

$C_{15}H_{15}NO_6$	calc.	C 59.02	H 4.92	N 4.59
(305.3)	found	58.84	5.07	4.73

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